The Role of Exercise Intensity and Protein Ingestion on Glycemic Control and the Risk of Hypoglycemia for Individuals with Type 1 Diabetes

Franklin Muntis

The University of North Carolina at Chapel Hill

Gillings School of Global Public Health

A paper submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Public Health in the Department of Nutrition

August 4th, 2020

Approved by: Elizabeth Mayer-Davis
(Paper Advisor)

Date: August 8, 2020

Specific Aims

Exercise is an essential component in type 1 diabetes (T1D) management yet approximately 60% of people with T1D do not participate in any structured exercise[1]. Exercise provides numerous benefits for those with T1D, such as improved body composition and glycemic control and a reduced risk of cardiovascular disease which is the leading cause of morbidity and mortality among young people with T1D[2]. For many with T1D, the fear of hypoglycemia during and following exercise is a major barrier to regular activity[3,4]. Exercise intensity and nutrient timing around exercise are assumed to be important factors in the risk of hypoglycemia in response to exercise, however, an understanding of their specific role is limited[5]. A better understanding of methods to mitigate the risk of hypoglycemia with exercise is imperative in engaging more people with T1D in regular exercise.

To address this critical need, we proposed to investigate the role of exercise intensity and peri-workout protein ingestion on the risk of hypoglycemia during and following exercise as well as the effect of exercise intensity on changes in glycemic control. Most individuals with T1D experience hypoglycemia within 45 minutes of beginning aerobic exercise and remain at an elevated risk of hypoglycemia for at least 24 hours following exercise[5]. Evidence suggests, however, that brief, high-intensity exercise such as high intensity interval training (HIIT) or resistance training tends to yield an increase in glycemia during and following exercise, likely due to an increased counter-regulatory response, and may contribute to increased glucose stability[5]. We hypothesize that intense aerobic or anaerobic exercise will lead to fewer occurrences of hypoglycemia during and following exercise and will contribute to greater time in range. Protein intake around exercise, a common strategy for the promotion of recovery, may also mitigate the risk of hypoglycemia in response to exercise[6]. Protein has been shown to increase glycemia through stimulating glucagon secretion and glucose production via gluconeogenesis which we hypothesize will reduce the risk of hypoglycemia during and following exercise. A greater understanding of these factors will help to establish potential strategies to attenuate the risk of hypoglycemia with exercise and empower individuals with T1D to improve their glycemic control through regular exercise. To assess these factors, we will utilize data from an ongoing trial (DP3DK113358, PI Mayer-Davis) of the effects of 3 different dietary patterns on glycemic control and weight loss among 82 overweight and obese young adults with T1D. We propose the following Specific Aims:

Aim 1. To establish the role of exercise intensity on the risk of hypoglycemia during and up to 4 hours following exercise. Heart rate and sRPE measures will be used to categorize exercise intensity. The occurrence of hypoglycemia during and following exercise will be assessed via Continuous Glucose Monitor (CGM)data allowing the elucidation of the role exercise intensity plays on hypoglycemia risk. It is hypothesized that greater time in intense aerobic or anaerobic exercise equivalent to an estimated 80% VO_2max (≥88% Age-Predicted MHR or sRPE ≥8) will be associated with fewer incidences of hypoglycemia.

Aim 2. To investigate the effect of a high protein meal within 2 hours before or after exercise on the risk of hypoglycemia during and up to 4 hours following exercise. 24 hour dietary recalls will be utilized to assess usual protein intake within 2 hours before or after exercise and CGM data will be assessed to identify the occurrence of hypoglycemia during and following exercise. It is hypothesized that the consumption of a high protein meal (≥25g protein) 2 hours prior to exercise will reduce the risk of hypoglycemia during and 4 hours following exercise. It is also hypothesized that a high protein meal within 2 hours after exercise cessation will reduce the risk of hypoglycemia up to 4 hours following exercise.

Aim 3. To elucidate the role of exercise intensity and peri-workout protein ingestion on glycemic excursions overnight and up to 24 following exercise. Heart rate and sRPE measures will be used to categorize exercise intensity and 24-hour dietary recalls will be used to determine protein ingestion within 2 hours of exercise. Time in range, Time below range and time above range will be assessed via CGM data. It is hypothesized that greater time in intense aerobic or anaerobic exercise equivalent to an estimated 80% VO_2max (≥88% Age-Predicted MHR or sRPE ≥8) will lead to greater time in range (70-180mg/dL) and reduced time below range (<70 mg/dl) overnight and 24 hours following exercise, but will also lead to greater time above range (181-250mg/dL). We also hypothesize that protein ingestion within 2 hours before or after exercise will contribute to greater time in range following exercise.

The proposed study will explore promising alternatives to traditional exercise and nutrition recommendations for people with T1D. Preliminary data suggests that exercising at higher intensities and consuming protein around exercise may help to ameliorate the risk of hypoglycemia experienced by many with T1D, however, our knowledge of their role is incomplete. The insights from this study may help to empower individuals with T1D to achieve greater levels of physical activity and garner greater interest in investigating new alternatives to traditional exercise and nutrition strategies in the field of diabetes research.

Research Strategy

1. Significance

1.1. Premise. Cardiovascular disease is the leading cause of mortality among young people with T1D[7,8]. Among patients with T1D, approximately 40% have hypertension, 60% have dyslipidemia and 60% are overweight or obese[1]. Physical activity plays a major role in reducing the risk of cardiovascular disease and other adverse health outcomes for people with T1D. A cross-sectional analysis of 18,028 adults with T1D found an inverse relationship between physical activity and HbA1c, diabetic ketoacidosis, BMI, dyslipidemia, hypertension, retinopathy or microalbuminuria, and severe hypoglycemia with coma[1].

A meta-analysis of the health benefits of physical activity for people with T1D found that regular exercise increased physical fitness and strength, reduced cardiovascular risk factors and daily insulin requirements and improved well-being in people with T1D[2]. They also highlighted, however, that the few randomized controlled trials reported have been small, of short duration and often did not control for diet and insulin dosing and that there was an urgent need for larger controlled trials that can provide guidance on the intensity, duration and type of exercise that will provide the greatest benefit for people with T1D. A further meta-analysis on the effects of exercise on acute and chronic glycemic control indicated that regular exercise, particularly aerobic exercise, contributed to better acute and chronic glycemic control in patients with T1D, however, there were only 2-3 studies investigating the effects of resistance training, high-intensity interval training or mixed training from which to calculate effect sizes for those types of exercise[9].

While there are many benefits to regular exercise in T1D, less than 20% of people with T1D report managing to perform aerobic exercise more than twice per week and approximately 60% report that they do not participate in any structured exercise[1]. The fear of hypoglycemia is a major barrier to exercise for many people with T1D[3,4,10,11]. Most people with T1D experience hypoglycemia within 45 minutes from the onset of aerobic exercise and remain at elevated risk of hypoglycemia for at least 24 hours following exercise[12–15]. In contrast, however, intense aerobic and anaerobic exercise and protein ingestion are both associated with rises in glycemia, however, their role in the prevention of hypoglycemia and promotion of greater time in range among individuals with T1D remains unclear.

1.2. Overarching Hypothesis. Our overarching hypothesis is that in overweight or obese young adults with T1D, greater time spent in intense aerobic or anaerobic exercise as well higher intake of protein within 2-hours of exercise will result in fewer incidences of hypoglycemia and greater time in range overnight and for 24 hours following exercise.

1.3. Innovation. Novel strategies are needed to equip people with T1D with the ability to overcome fear of hypoglycemia and to safely engage in regular exercise. Few studies have examined the effects of intense aerobic or anaerobic exercise on time in range and the risk of hypoglycemia. While preliminary data suggest an attenuated decrease in glycemia during and acutely following exercise with the inclusion of intense aerobic and anaerobic exercise, the results on the effects of intensity of exercise on nocturnal hypoglycemia remains mixed indicating the need for further research[5,9,16–22]. Furthermore, while protein ingestion has been shown to have a delayed post-prandial hyperglycemic effect and has been shown to be protective against hypoglycemia, however, to our knowledge no studies have been conducted on the effects of protein timing around exercise on time in range and the risk of post-exercise hypoglycemia in people with T1D.

1.4 Aim 1 and Aim 3a Exercise Intensity on Glycemic Excursions. Aerobic exercise causes a decrease in glycemia in people with T1D with most experiencing hypoglycemia within 45 minutes of beginning aerobic exercise and remaining at elevated risk of hypoglycemia for at least 24 hours following exercise[12–15]. The incorporation of brief, high intensity exercise, such as resistance training or high intensity interval training (HIIT), has been proposed as a means of promoting improvements in cardiometabolic health while reducing the risk of hypoglycemia following exercise[22]. Resistance exercise and high intensity interval training have both been associated with better glucose stability and attenuated decreases in glycemia during and acutely following exercise compared to moderate intensity aerobic[23–25]. Furthermore, inclusion of brief, high intensity intervals or resistance training prior to aerobic exercise has been shown to reduce the decline in blood glucose

associated following aerobic exercise[26,27]. While the finds on acute changes in glycemia are promising, the effects of intense aerobic or anaerobic exercise on the risk of nocturnal hypoglycemia has been mixed with studies some studies indicating a possible protective effect[18,19,25] and suggesting an increased risk of hypoglycemia at increased intensities of exercise [20,28]. As such, we plan to investigate the effects of increasing exercise intensity on both acute (during and 4 hours following exercise) and delayed glycemic excursions (overnight and 24 hours following exercise). Overall, intense aerobic and anaerobic exercise are associated with increased glycemia for hours following exercise, likely contributable to an increased catecholamine response to higher intensity exercise[5]. It is our hypothesis that greater time spent in intense aerobic or anaerobic exercise will yield greater time in range and a reduced risk of hypoglycemia during and up to 24 hours following exercise.

1.5 Aim 2 and Aim 3b Protein Ingestion on Glycemic Excursion. Peri-workout protein ingestion has been shown to have many benefits. Protein ingestion following endurance training has been associated with reduced myofibrillar damage and reduced muscle soreness, greater effects seen when included as a protein carbohydrate mix[29–32]. Furthermore, resistance exercise has been shown to enhance muscle amino acid sensitivity of myofibrillar protein synthesis (MPS) following exercise reaching a peak around 3 hours post exercise and remaining elevated for 24-72 hours after[33]. Protein ingestion during this time of increased muscle sensitivity has has shown to increase MPS by 30 – 100% providing a positive muscle protein balances[32]. Meta-analyses on the effects of pooled data on protein supplementation of 15-25g following exercise have found significant improvements in muscular strength and performance when paired with resistance exercise[32,34,35]. Protein ingestion paired with resistance exercise may also yield greater improvements in muscle mass and greater reductions in fat mass when paried with a hypercaloric or hypocaloric diet, respectively[32,34,36–42]. Current recommendations for post-workout protein ingestion to maximize the protein synthetic response to exercise are approximately 0.25g/kg or an absolute intake of 20-40g protein[32]. In addition to the improved adaptations to exercise outlined, peri-workout protein intake may also promote improved glycemic control for individuals with T1D. Intensive insulin therapy, an essential part of diabetes management, utilizes algorithms based solely on carbohydrate intake[43]. While carbohydrates are the predominate macronutrient affecting post-prandial blood glucose, protein and fat have also been shown to contribute to post-prandial increases in glycemia[6,43,44]. In healthy populations, protein intake is associated with concurrent increases in insulin and glucagon, but not blood glucose. In T1D, however, protein stimulates increased hepatic glucose production that is not counteracted by a simultaneous increase in insulin secretion thus leading to increased glycemia and insulin requirements[6]. In children with T1D, meals high in protein or fat where found to increase post-prandial blood glucose from 3 hours to 5 hours post-meal and the effects of the macronutrients were found to be additive[43]. Protein ingestion in this study was also found to be protective against hypoglycemia[43]. Similarly, in adults with T1D, the ingestion of meals containing between 28g and 57g of additional protein have yielded similar post-prandial glycemic responses and insulin requirements[45,46]. Furthermore, the ingestion of 28g of protein in a mixed meal or 75g of protein alone have been shown to result in significant and sustained hyperglycemia commencing 2-3 hours following exercise and continuing beyond 5 hours[6,44,47]. It is clear that protein ingestion plays a role in post-prandial glycemic excursions, however, how timing of protein ingestion around exercise may alter time in range and the risk of exercise-induced hypoglycemia has yet to be investigated. We hypothesize that ingestion of a high protein meal within 2 hours prior of exercise will yield a reduced risk of hypoglycemia during exercise and the consumption of a high protein meal within 2 hours prior or following exercise will lead to greater time in range following exercise and a reduce risk of hypoglycemia up to 24 hours following exercise.

1.6 Summary of Significance. Our study is highly in innovative in that it would be the first study to investigate the role of peri-workout protein ingestion on time in range and the risk of hypoglycemia following exercise. It also addresses an urgent need for greater information on the role of exercise intensity on glycemic control and risk of hypoglycemia during and following exercise. We expect that greater intensity of aerobic or anaerobic exercise will contribute to a reduced risk of hypoglycemia during and following exercise (Aim 1) and greater glycemic control as measured by time in range (Aim 3a). Furthermore, we expect that peri-workout protein ingestion will similarly result in a reduced risk of hypoglycemia during and following exercise (Aim 2) and will result in greater time in range (Aim 3b). To our knowledge, no other studies have investigated the role of protein ingestion around exercise on glycemic excursions during and following exercise in T1D Furthermore, reviews of physical activity trials in T1D have indicated a need for greater understanding of the role of exercise intensity on glycemic control and the risk of hypoglycemia. **Determining the role of aerobic and anaerobic exercise intensity and of protein intake will contribute to the development of innovative strategies to**

mitigate the risk of exercise-induced hypoglycemia and empower people with T1D to experience the benefits of regular exercise.

2. Approach: The following sections describe: 1) the NIH-funded study called ACT1ON, 2) the pilot physical activity data collection effort that was added to the ACT1ON protocol midway through the study that is the subject of these aims, and 3) the statistical analyses proposed for this F31 training grant.

2.1. ACT1ON study (1DP3DK113358-02, contact PI Mayer-Davis). Prior research has demonstrated effectiveness of various diets for co-managing weight and HbA1c in T2D; however, no T1D-specific guidelines exist. A rigorous adaptive design is underway to establish estimates of the effect of a diet intervention in young adults with overweight or obesity and T1D. The goal of this funded Sequential Multiple Assignment Randomized Trial is to assess acceptability and adherence to three evidence-based diets and to estimate effect sizes for weight and glycemia to construct a fully powered randomized controlled trial (RCT), including collection/analysis of measures in the funded ancillary aims.

Methods: Following baseline data collection and a two-week run-in, participants (Total n=69, UNC-CH (40), Stanford (29)) are randomized to one of three diets: Mediterranean without calorie restriction,[48,49] hypocaloric low-carbohydrate (~15-20% calories from carbohydrate),[50] and hypocaloric moderate fat (~30% calories from fat).[51] Behavioral counseling, carbohydrate counting for insulin dosing, and encouragement of physical activity are the same across the diets. Potential re-randomization periods are at three- and six-months; participants are re-randomized if the diet is unacceptable to the participant, or if glycemic (increase in HbA1c of ≥ 0.5%) or weight (achieving <2% body weight loss, unless "normal weight" status achieved [BMI < 25]) targets are not met. The intervention period is nine months. Registered dietitians conduct 18 sessions, including phone check-ins. Dietitians are centrally trained in Motivational Interviewing and Problem Solving Skills Training.

Inclusion/exclusion criteria and recruitment: Individuals ages 19-30 with >1 year duration of T1D, BMI 27-39.9, and HbA1c <13% are included. Exclusion criteria: pregnant women, diagnosed eating disorder, and other conditions rendering participation inappropriate. 42 participants/site (3-4/month over 12 months) are recruited.

Standardized Measurements (baseline & 3-, 6-, and 9-months post randomization):

Glycemic control: Participants are provided with a Abbott Freestyle LibrePro continuous glucose monitor (CGM) which is a flash glucose monitoring system FDA approved for use by adults 18 years of age and older. Blinded continuous glucose monitoring (CGM) will be used to assess short-term glycemia, including frequency and time spent in hypoglycemia, as well as time in range, above range, and below range during the 14 day wear time at each measurement visit. Consistent with a report on consensus measurements of glycemia we define hypoglycemia as CGM-based glucose <70mg/dl for more than 10 min, not requiring help from another person, time in range as percent daily time spent in a blood glucose range of 70-180 mg/dL, percent time above range as daily time spent above 180 mg/dL and time below range as the percent time below 70 mg/dL target[52]. As part of the virtual transition of the ACT1ON study in response to Covid-19, HbA1c will provide a measure of long-term glycemic control.

Adiposity: Percent body fat and visceral adipose volume (in^3) are estimated with DXA.

Weight status: Anthropometry follows standard procedures for determination of BMI.

Dietary Intake: 24-hour dietary recalls (two unannounced days per data collection time point) are obtained by telephone by trained and certified interviewers from the UNC NIH/NIDDK Nutrition Obesity Research Center staff (P30DK056350; MPI Mayer-Davis) under the direction of Dr. Mayer-Davis (Diet Assessment Core Director), using the Nutrient Data System for Research (NDSR) software and the multiple pass interviewing method[53,54]. Habitual dietary patterns are also assessed using a validated food frequency questionnaire (NCI Diet History Questionnaire II http://riskfactor.cancer.gov/dhq2/webquest/).

Acceptability of Experimental Diets: No instrument to systematically assess acceptability of experimental diets could be identified, so we developed a 5-item questionnaire for this purpose (Cronbach alpha = 0.89).

Physical Activity: The validated[55,56] Previous Day Physical Activity Recall (PDPAR) divides the day into half-hour time blocks and queries the dominant activity and the approximate intensity of that activity for that period, categorized as ''light,'' ''medium,'' ''hard,'' or ''very hard.'' The PDPAR will be under the direction of the UNC NORC, to be administered concurrent with the 24-hour dietary recalls, as we have done previously.[57]

Additional measures: Other measures being obtained include surveys to evaluate ingestive behavior and nutrition knowledge, diabetes quality of life and fear of hypoglycemia.

Statistical Analyses and Power: The primary goal for the ACT1ON study is to evaluate the feasibility of the three diet interventions and estimate potential effect size and variance for a future randomized controlled trial. The ACT1ON study analyses also seek to assess the effect of experimental diets on adiposity (percent body

fat and BMI) and glycemic control (time in range and HbA1c). Based on previous reports,[58,59] the study has 80% power to detect a 3.0 kg weight change and 1.3% HbA1c change.

Data Management: An online data management system from the UNC Collaborative Studies Coordinating Center has been developed for the parent study and includes ancillary study data. The system includes online data collection and participant randomization tracking. The secure server environment is located within a hardened data center on UNC campus, and is governed by UNC information security guidelines. **ACT1ON Progress:** In response to the Covid-19 pandemic, the ACT1ON study was turned into a completely remote protocol for intervention and analysis. The ACT1ON study was designed with capacity for telehealth delivery with online data collection forms, home Bluetooth enabled scales provided to participants, and approval for remote RD visits. Following Covid-19, participants were provided CGM via mails as well as capillary tube collection kits for home HbA1c collection. Furthermore, instructions are now provided via zoom and home scales are being utilized for standardized weight measures. The primary changes to the study was the removal of DXA body composition measurement and the stopping of enrollment at prior to the original target of 84 participants (Total (n=69), UNC-CH (n=40) Stanford (n=29)).

2.2. Pilot Physical Activity Data Selection

Description: Data collection for the physical activity pilot began at both UNC-CH and Stanford as part of remote data collection for the ACT1ON trial in June 2020. The goal of the physical activity pilot is to assess the role of varying amounts and intensities of physical activity on the primary outcomes of glycemic control and weight management.

Inclusion/Exclusion Criteria: Any participant in the ACT1ON SMART pilot willing to provide data regarding their physical activity is invited to participate. Of the 69 participants of the ACT1ON study (UNC-CH=40, Stanford = 29) that will be recruited, we expect that 65 (94%) will participate in the physical activity portion of the protocol. Multiple observations will be obtained for participants over the 14-day wear time across multiple study visits for participants with greater than one measurement visit remaining. It is estimated

Methods: Consent to participate in the Physical Activity Pilot is obtained remotely from participants as part of preparation for their next upcoming standardized measurement visit. Participants in the physical activity pilot are asked to wear a Garmin Vivosmart 4 Fitness Tracker and provide a session rate of perceived exertion (sRPE) rating with each bout of structured exercise during each 14-day data collection period, concurrent with CGM data collection. Session Rate of Perceived Exertion (sRPE) is assessed by participants utilizing a secure online survey containing a validated sRPE scale. The scale is made accessible to participants through a QR code printed on labels attached to a water bottle and keychain provided to the participants by the study site. Participants are asked to wait at least 30 minutes following exercise to assess their sRPE, but within 24 hours in accordance with previous studies which found that sRPE measures collected earlier than 30 minutes had an increased risk of bias by the last exercise done in the session, but were valid up to 24 hours following exercise. Participants also receive a daily email reminder during the 14-day data collection period that contains a link to the survey.

Additional Measures:

Garmin Vivosmart 4 Fitness Tracker: The Garmin Vivosmart 4 fitness tracker utilizes a built in Garmin Elevate™ Heart Rate monitor, altimeter, accelerometer, and Bluetooth® Smart and ANT+® technology to measure outcomes of interest, including heart rate (HR), step count, floors climbed, and energy expenditure (EE) and automatically syncs to a study Garmin Connect account. Extraction and overlaying of Garmin Data with CGM data will be performed by a pediatric endocrinologist in contract with the ACT1ON team.

Heart Rate: Heart rate has been shown to have an almost linear relationship with VO_2max at submaximal intensities and is one of the most common objective tools for the measurement of exercise intensity[60]. Heart rate is collected by the wrist-worn Garmin Vivosmart4 fitness tracker which has been shown to be validated as an accurate tool and possess an activity mode which has been shown to improve accuracy of heart rate during exercise[61]. Intense aerobic or anerobic exercise is characterized as exercise at ≥80% estimated VO_2max equivalent to approximately 88% age-predicted HRmax[62].

Session Rate of Perceived Exertion (sRPE): sREP has been shown to be a valid, reliable, and practical tool for monitoring training load[63–66]. This method asks participants to assess the intensity of their workout with a single number rating between 0 – 10, with 0 being equivalent to complete rest and 10 being a maximal bout of exercise. Through incorporating both RPE and duration of exercise, this method can provide insight to the physical and psychological effort of exercise over the course of 14 days, as well as the total strain and monotony of training experienced by participants. sRPE data is recorded via a survey accessible to participants via a QR code provide to the participants with their study materials. Responses to sRPE surveys are stored and extracted from a secure database (REDCap).

2.3. Statistical Considerations

Table 1: Detectable effects (Partial R^2) at 80% and 90% power, $\alpha = 0.05$†	80% power	90% power
Aim 1 & 3a. Cross-Sectional Time in Intense Aerobic or Anaerobic Exercise vs Risk of Hypoglycemia During and 4 Hours Following Exercise	0.10	0.13
Aim 2 & 3b. Cross-sectional Peri-Workout Protein Intake vs Occurrence of Hypoglycemia During and 4 Hours Following Exercise	0.10	0.13
Aim 3a. Cross Sectional Time in Intense Aerobic or Anaerobic Exercise vs Time in Range 24 Hours Following Exercise	0.10	0.13
Aim 3b. Cross Sectional Peri-Workout Protein Intake vs Time in Range 24 Hours Following Exercise	0.10	0.13
†Effect sizes computed for partial R^2 with G-Power software Version 3.1.9.7.		

Significant effects in prior studies with comparable or smaller sample sizes
Aim 1 and 3a. Exercise Intensity and Risk of Hypoglycemia During and 4-Hours Following Exercise: In 7 adult men with T1D, high intensity interval training exercise resulted in significantly smaller decrease in blood glucose than continuous exercise (1.51 ± 0.92 vs. 3.00 ± 1.54 mmol.l-1, p = 0.024)[28]. Furthermore, In 11 adults with T1D, the addition of intermittent, high intensity work to continuous exercise resulted in significantly high nocturnal glucose levels, less post-exercise hypoglycemia (5.2 vs 1.5% of time spent with glucose <4.0 mmol/L) and more post-exercise hyperglycemia (33.8 vs. 20.4% of time > 11.0 mmol/l) compared to continuous exercise alone[18].

Aim 2 and 3b. Protein Ingestion & Hypoglycemia During and 4-Hours Following Exercise: In 33 children with T1D, consumption of a high protein meal had a protective effect on the development of hypoglycemia over 5 hours (Odds Ratio 0.16, 95% CI 0.06 – 0.41)[43].

Statistical Analyses:
Demographic, clinical, and design covariates (Baseline & 3-, 6-, & 9-month): Ns, means, and SDs will be computed for continuous variables (age and insulin dose per kg). Counts and percentages will be computed for categorical variables [sex, race/ethnicity, insulin regimen, site, and randomized diet (3-, 6-, and 9-months).
Exposures and Outcomes **(Table 2)**
3-, 6-, and 9-month Measurement Visits: Time in intense aerobic or anaerobic exercise, protein intake within 2 hours of exercise, occurrence of hypoglycemia, time in range, time above range and time below range following exercise will be cross-sectionally analyzed for each measurement visit.

Table 2. Proposed Study Variable Descriptions and Measurement Time Points

AIMS 1 & 3a	Measure(s)	Description	3-mo	6-mo	9-mo
Exposure	Time in Intense Aerobic & Anaerobic Exercise	Exercise reaching a peak HR ≥88% of age-predicted heart rate max or a reported sRPE ≥8.	X	X	X
Outcomes (AIM 1)	Occurrence of hypoglycemia during exercise	CGM-based glucose <70mg/dl for more than 10 min, not requiring help from another person, during exercise	X	X	X
	Occurrence of hypoglycemia within 4 hours following exercise	CGM-based glucose <70mg/dl for more than 10 min, not requiring help from another person within 4 hours following exercise	X	X	X
Outcomes (AIM 3a)	Time in range	% time spent in 70–180 mg/dl during and 24 hours following exercise	X	X	X
	Time above range	% time spent >180 mg/dl during and 24 hours following exercise	X	X	X
	Time below range	% time spent <70 mg/dl during and 24 hours following exercise	X	X	X
AIMs 2 & 3b	**Measure(s)**	**Description**	**3-mo**	**6-mo**	**9-mo**
Exposure	Peri-Workout Protein Ingestion	Consumption of a meal containing at least 25g protein within 2 hours before or following exercise.	X	X	X

Outcomes (Aim 2)	Occurrence of hypoglycemia during exercise	CGM-based glucose <70mg/dl for more than 10 min, not requiring help from another person during exercise	X	X	X
	Occurrence of hypoglycemia within 4 hours following exercise	CGM-based glucose <70mg/dl for more than 10 min, not requiring help from another person within 4 hours following exercise	X	X	X
Outcomes (AIM 3b)	Time in range	% time spent in 70–180 mg/dl during and 24 hours following exercise	X	X	X
	Time above range	% time spent >180 mg/dl during and 24 hours following exercise	X	X	X
	Time below range	% time spent <70 mg/dl during and 24 hours following exercise	X	X	X
Potential confounders	Demographic (**all aims**)	Age, gender, race/ethnicity, clinic site	X		
	Clinical (**all aims**)	Age at diagnosis, insulin regimen, randomized diet*	X		
	Dietary (**Aims 2 and 3b)**	Kcal, Fat and Carbohydrate Intake	X	X	X
	Exercise Factors **(Aims 1 & 3a)**	Exercise duration	X	X	X

Inferential Analysis and Expected Outcomes:
Linear mixed models that account for non-independence of observations due to repeated measures within individuals will be used to evaluate study hypotheses. To account for confounding, we will include covariates in models if they alter effect estimates or standard error substantially (i.e., by $\geq$ 10% of the unadjusted value). For all models, following calculation of unadjusted estimates (Model 1), we will explore confounding through adjustment for prespecified demographic (Model 2) and clinical (Model 3) covariates

2.4 Challenges and Opportunities
With current recruitment numbers we possess sufficient sample size to detect an effect for our primary outcomes, however, the Covid-19 pandemic has limited recruitment below originally intended targets. Furthermore, while the study has been adapted to be fully virtual, as participants manage the additional stress of Covid-19, retention of participants within the study may become more difficult. The results from this study, however, will provided further insight into the role of exercise intensity on the risk of hypoglycemia and time in range for young adults with T1D and would be the first study to assess the effects of protein timing around exercise on the these same outcomes. Such insights are needed to inform strategies for mitigating the risk of hypoglycemia during and following exercise for people with T1D that may help to empower individuals with T1D to achieve higher levels of physical activity.

3. Summary The proposed aims and methods represent a rigorous and reproducible model for collecting pilot data on the relationship between exercise intensity and peri-workout protein intake on the risk of hypoglycemia and glycemic excursions following exercise in a weight management trial of young adults with T1D. Hypoglycemia and glycemic excursions following exercise remain a significant barrier to exercise for people with T1D. The results of the proposed study will advance our knowledge of the role of two potential factors that may help to mitigate the risk of hypoglycemia during and following exercise for those with T1D. Furthermore, the results of the proposed study will drive future research that may inform clinical practice guidelines and empower people with T1D to engage in greater levels of physical activity.

Bibliography

1. Bohn B, Herbst A, Pfeifer M, et al. Impact of Physical Activity on Glycemic Control and Prevalence of Cardiovascular Risk Factors in Adults With Type 1 Diabetes: A Cross-sectional Multicenter Study of 18,028 Patients. *Diabetes Care*. 2015;38(8):1536-1543. doi:10.2337/dc15-0030

2. Quirk H, Blake H, Tennyson R, Randell TL, Glazebrook C. Physical activity interventions in children and young people with Type 1 diabetes mellitus: a systematic review with meta-analysis. *Diabet Med*. 2014;31(10):1163-1173. doi:10.1111/dme.12531

3. Brazeau A-S, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. *Diabetes Care*. 2008;31(11):2108-2109. doi:10.2337/dc08-0720

4. Addala A, Igudesman D, Kahkoska AR, et al. The interplay of type 1 diabetes and weight management: A qualitative study exploring thematic progression from adolescence to young adulthood. *Pediatr Diabetes*. 2019;20(7):974-985. doi:10.1111/pedi.12903

5. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol*. 2017;5(5):377-390. doi:10.1016/S2213-8587(17)30014-1

6. Paterson M, Bell KJ, O'Connell SM, Smart CE, Shafat A, King B. The role of dietary protein and fat in glycaemic control in type 1 diabetes: implications for intensive diabetes management. *Curr Diab Rep*. 2015;15(9):61. doi:10.1007/s11892-015-0630-5

7. Miller RG, Mahajan HD, Costacou T, Sekikawa A, Anderson SJ, Orchard TJ. A contemporary estimate of total mortality and cardiovascular disease risk in young adults with type 1 diabetes: the pittsburgh epidemiology of diabetes complications study. *Diabetes Care*. 2016;39(12):2296-2303. doi:10.2337/dc16-1162

8. Katz M, Giani E, Laffel L. Challenges and opportunities in the management of cardiovascular risk factors in youth with type 1 diabetes: lifestyle and beyond. *Curr Diab Rep*. 2015;15(12):119. doi:10.1007/s11892-015-0692-4

9. Tonoli C, Heyman E, Roelands B, et al. Effects of different types of acute and chronic (training) exercise on glycaemic control in type 1 diabetes mellitus: a meta-analysis. *Sports Med*. 2012;42(12):1059-1080. doi:10.2165/11635380-000000000-00000

10. Lascar N, Kennedy A, Hancock B, et al. Attitudes and barriers to exercise in adults with type 1 diabetes (T1DM) and how best to address them: a qualitative study. *PLoS One*. 2014;9(9):e108019. doi:10.1371/journal.pone.0108019

11. Jabbour G, Henderson M, Mathieu M-E. Barriers to Active Lifestyles in Children with Type 1 Diabetes. *Can J Diabetes*. 2016;40(2):170-172. doi:10.1016/j.jcjd.2015.12.001

12. García-García F, Kumareswaran K, Hovorka R, Hernando ME. Quantifying the acute changes in glucose with exercise in type 1 diabetes: a systematic review and meta-analysis. *Sports Med*. 2015;45(4):587-599. doi:10.1007/s40279-015-0302-2

13. Tansey MJ, Tsalikian E, Beck RW, et al. The effects of aerobic exercise on glucose and counterregulatory hormone concentrations in children with type 1 diabetes. *Diabetes Care*. 2006;29(1):20-25. doi:10.2337/diacare.29.1.20

14. Riddell MC, Bar-Or O, Ayub BV, Calvert RE, Heigenhauser GJ. Glucose ingestion matched with total carbohydrate utilization attenuates hypoglycemia during exercise in adolescents with IDDM. *International Journal of Sport Nutrition and Exercise Metabolism*. 1999;9(1):24-34.

15. Gomez AM, Gomez C, Aschner P, et al. Effects of performing morning versus afternoon exercise on glycemic control and hypoglycemia frequency in type 1 diabetes patients on sensor-augmented insulin pump therapy. *J Diabetes Sci Technol*. 2015;9(3):619-624. doi:10.1177/1932296814566233

16. Riddell M, Pooni R, Brown RE, et al. Variability and reproducibility in the rise in blood glucose levels in response to high intensity interval training (HIIT) in type 1 diabetes (t1d)—the FIT reproducibility study. *Diabetes*. 2018;67(Supplement 1):744-P. doi:10.2337/db18-744-P

17. Riddell MC, Pooni R, Yavelberg L, et al. Reproducibility in the cardiometabolic responses to high-intensity interval exercise in adults with type 1 diabetes. *Diabetes Res Clin Pract*. 2019;148:137-143. doi:10.1016/j.diabres.2019.01.003

18. Iscoe KE, Riddell MC. Continuous moderate-intensity exercise with or without intermittent high-intensity work: effects on acute and late glycaemia in athletes with Type 1 diabetes mellitus. *Diabet Med*. 2011;28(7):824-832. doi:10.1111/j.1464-5491.2011.03274.x

19. Scott SN, Cocks M, Andrews RC, et al. Fasted High-Intensity Interval and Moderate-Intensity Exercise Do Not Lead to Detrimental 24-Hour Blood Glucose Profiles. *J Clin Endocrinol Metab*. 2019;104(1):111-117. doi:10.1210/jc.2018-01308

20. Maran A, Pavan P, Bonsembiante B, et al. Continuous glucose monitoring reveals delayed nocturnal hypoglycemia after intermittent high-intensity exercise in nontrained patients with type 1 diabetes. *Diabetes Technol Ther*. 2010;12(10):763-768. doi:10.1089/dia.2010.0038

21. Rooijackers HM, Wiegers EC, van der Graaf M, et al. A Single Bout of High-Intensity Interval Training Reduces Awareness of Subsequent Hypoglycemia in Patients With Type 1 Diabetes. *Diabetes*. 2017;66(7):1990-1998. doi:10.2337/db16-1535

22. Farinha JB, Krause M, Rodrigues-Krause J, Reischak-Oliveira A. Exercise for type 1 diabetes mellitus management: General considerations and new directions. *Med Hypotheses*. 2017;104:147-153. doi:10.1016/j.mehy.2017.05.033

23. Yardley JE, Kenny GP, Perkins BA, et al. Resistance versus aerobic exercise: acute effects on glycemia in type 1 diabetes. *Diabetes Care*. 2013;36(3):537-542. doi:10.2337/dc12-0963

24. Guelfi KJ, Ratnam N, Smythe GA, Jones TW, Fournier PA. Effect of intermittent high-intensity compared with continuous moderate exercise on glucose production and utilization in individuals with type 1 diabetes. *Am J Physiol Endocrinol Metab*. 2007;292(3):E865-70. doi:10.1152/ajpendo.00533.2006

25. Scott SN, Cocks M, Andrews RC, et al. High-Intensity Interval Training Improves Aerobic Capacity Without a Detrimental Decline in Blood Glucose in People With Type 1 Diabetes. *J Clin Endocrinol Metab*. 2019;104(2):604-612. doi:10.1210/jc.2018-01309

26. Yardley JE, Kenny GP, Perkins BA, et al. Effects of performing resistance exercise before versus after aerobic exercise on glycemia in type 1 diabetes. *Diabetes Care*. 2012;35(4):669-675. doi:10.2337/dc11-1844

27. Bussau VA, Ferreira LD, Jones TW, Fournier PA. A 10-s sprint performed prior to moderate-intensity exercise prevents early post-exercise fall in glycaemia in individuals with type 1 diabetes. *Diabetologia*. 2007;50(9):1815-1818. doi:10.1007/s00125-007-0727-8

28. Moser O, Tschakert G, Mueller A, et al. Effects of High-Intensity Interval Exercise versus Moderate Continuous Exercise on Glucose Homeostasis and Hormone Response in Patients with Type 1 Diabetes Mellitus Using Novel Ultra-Long-Acting Insulin. *PLoS One*. 2015;10(8):e0136489. doi:10.1371/journal.pone.0136489

29. Saunders MJ, Kane MD, Todd MK. Effects of a carbohydrate-protein beverage on cycling endurance and muscle damage. *Med Sci Sports Exerc*. 2004;36(7):1233-1238. doi:10.1249/01.mss.0000132377.66177.9f

30. Saunders MJ, Luden ND, Herrick JE. Consumption of an oral carbohydrate-protein gel improves cycling endurance and prevents postexercise muscle damage. *J Strength Cond Res*. 2007;21(3):678-684. doi:10.1519/R-20506.1

31. D'Lugos AC, Luden ND, Faller JM, Akers JD, McKenzie AI, Saunders MJ. Supplemental Protein during Heavy Cycling Training and Recovery Impacts Skeletal Muscle and Heart Rate Responses but Not Performance. *Nutrients*. 2016;8(9). doi:10.3390/nu8090550

32. Jäger R, Kerksick CM, Campbell BI, et al. International Society of Sports Nutrition Position Stand: protein and exercise. *J Int Soc Sports Nutr*. 2017;14:20. doi:10.1186/s12970-017-0177-8

33. Burd NA, West DWD, Moore DR, et al. Enhanced amino acid sensitivity of myofibrillar protein synthesis persists for up to 24 h after resistance exercise in young men. *J Nutr*. 2011;141(4):568-573. doi:10.3945/jn.110.135038

34. Pasiakos SM, McLellan TM, Lieberman HR. The effects of protein supplements on muscle mass, strength, and aerobic and anaerobic power in healthy adults: a systematic review. *Sports Med*. 2015;45(1):111-131. doi:10.1007/s40279-014-0242-2

35. Cermak NM, Res PT, de Groot LCPGM, Saris WHM, van Loon LJC. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. *Am J Clin Nutr*. 2012;96(6):1454-1464. doi:10.3945/ajcn.112.037556

36. Naclerio F, Larumbe-Zabala E. Effects of Whey Protein Alone or as Part of a Multi-ingredient Formulation on Strength, Fat-Free Mass, or Lean Body Mass in Resistance-Trained Individuals: A Meta-analysis. *Sports Med*. 2016;46(1):125-137. doi:10.1007/s40279-015-0403-y

37. Tipton KD, Phillips SM. Dietary protein for muscle hypertrophy. *Nestle Nutr Inst Workshop Ser*. 2013;76:73-84. doi:10.1159/000350259

38. Phillips SM. The science of muscle hypertrophy: making dietary protein count. *Proc Nutr Soc*. 2011;70(1):100-103. doi:10.1017/S002966511000399X

39. Kreider RB, Serra M, Beavers KM, et al. A structured diet and exercise program promotes favorable changes in weight loss, body composition, and weight maintenance. *J Am Diet Assoc*. 2011;111(6):828-843. doi:10.1016/j.jada.2011.03.013

40. Layman DK, Evans E, Baum JI, Seyler J, Erickson DJ, Boileau RA. Dietary protein and exercise have additive effects on body composition during weight loss in adult women. *J Nutr*. 2005;135(8):1903-1910. doi:10.1093/jn/135.8.1903

41. Pasiakos SM, Cao JJ, Margolis LM, et al. Effects of high-protein diets on fat-free mass and muscle protein synthesis following weight loss: a randomized controlled trial. *FASEB J*. 2013;27(9):3837-3847. doi:10.1096/fj.13-230227

42. Kerksick CM, Wismann-Bunn J, Fogt D, et al. Changes in weight loss, body composition and cardiovascular disease risk after altering macronutrient distributions during a regular exercise program in obese women. *Nutr J*. 2010;9:59. doi:10.1186/1475-2891-9-59

43. Smart CEM, Evans M, O'Connell SM, et al. Both dietary protein and fat increase postprandial glucose excursions in children with type 1 diabetes, and the effect is additive. *Diabetes Care*. 2013;36(12):3897-3902. doi:10.2337/dc13-1195

44. Paterson MA, Smart CEM, Lopez PE, et al. Influence of dietary protein on postprandial blood glucose levels in individuals with Type 1 diabetes mellitus using intensive insulin therapy. *Diabet Med*. 2016;33(5):592-598. doi:10.1111/dme.13011

45. Peters AL, Davidson MB. Protein and fat effects on glucose responses and insulin requirements in subjects with insulin-dependent diabetes mellitus. *Am J Clin Nutr*. 1993;58(4):555-560. doi:10.1093/ajcn/58.4.555

46. García-López JM, González-Rodriguez M, Pazos-Couselo M, Gude F, Prieto-Tenreiro A, Casanueva F. Should the amounts of fat and protein be taken into consideration to calculate the lunch prandial insulin bolus? Results from a randomized crossover trial. *Diabetes Technol Ther*. 2013;15(2):166-171. doi:10.1089/dia.2012.0149

47. Paterson MA, Smart C, Mcelduff P, et al. Influence of pure protein on postprandial blood glucose levels in individuals with type 1 diabetes mellitus. In: Vol 63. AMER DIABETES ASSOC 1701 N BEAUREGARD ST, ALEXANDRIA, VA 22311-1717 USA; 2014:A15-A15.

48. Lasa A, Miranda J, Bulló M, et al. Comparative effect of two Mediterranean diets versus a low-fat diet on glycaemic control in individuals with type 2 diabetes. *Eur J Clin Nutr*. 2014;68(7):767-772. doi:10.1038/ejcn.2014.1

49. Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2013;36(11):3821-3842. doi:10.2337/dc13-2042

50. Tay J, Luscombe-Marsh ND, Thompson CH, et al. Comparison of low- and high-carbohydrate diets for type 2 diabetes management: a randomized trial. *Am J Clin Nutr*. 2015;102(4):780-790. doi:10.3945/ajcn.115.112581

51. American Diabetes Association. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes care*. 2007;30(6):1374-1383.

52. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care*. 2019;42(8):1593-1603. doi:10.2337/dci19-0028

53. Posner BM, Smigelski C, Duggal A, Morgan JL, Cobb J, Cupples LA. Validation of two-dimensional models for estimation of portion size in nutrition research. *Journal of the American Dietetic Association (USA)*. 1992.

54. Beaton GH, Milner J, Corey P, et al. Sources of variance in 24-hour dietary recall data: implications for nutrition study design and interpretation. *Am J Clin Nutr*. 1979;32(12):2546-2559. doi:10.1093/ajcn/32.12.2546

55. Clark BK, Pavey TG, Lim RF, Gomersall SR, Brown WJ. Past-day recall of sedentary time: Validity of a self-reported measure of sedentary time in a university population. *J Sci Med Sport*. 2016;19(3):237-241. doi:10.1016/j.jsams.2015.02.001

56. Kozey Keadle S, Lyden K, Hickey A, et al. Validation of a previous day recall for measuring the location and purpose of active and sedentary behaviors compared to direct observation. *Int J Behav Nutr Phys Act*. 2014;11:12. doi:10.1186/1479-5868-11-12

57. Maahs DM, Mayer-Davis E, Bishop FK, Wang L, Mangan M, McMurray RG. Outpatient assessment of determinants of glucose excursions in adolescents with type 1 diabetes: proof of concept. *Diabetes Technol Ther*. 2012;14(8):658-664. doi:10.1089/dia.2012.0053

58. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N Engl J Med*. 2014;371(4):313-325. doi:10.1056/NEJMoa1314474

59. Wing RR, Tate DF, Espeland MA, et al. Innovative Self-Regulation Strategies to Reduce Weight Gain in Young Adults: The Study of Novel Approaches to Weight Gain Prevention (SNAP) Randomized Clinical Trial. *JAMA Intern Med*. 2016;176(6):755-762. doi:10.1001/jamainternmed.2016.1236

60. Achten J, Jeukendrup AE. Heart rate monitoring: applications and limitations. *Sports Med*. 2003;33(7):517-538.

61. Reddy RK, Pooni R, Zaharieva DP, et al. Accuracy of Wrist-Worn Activity Monitors During Common Daily Physical Activities and Types of Structured Exercise: Evaluation Study. *JMIR Mhealth Uhealth*. 2018;6(12):e10338. doi:10.2196/10338

62. Swain DP, Abernathy KS, Smith CS, Lee SJ, Bunn SA. Target heart rates for the development of cardiorespiratory fitness. *Med Sci Sports Exerc*. 1994;26(1):112-116.

63. Day ML, McGuigan MR, Brice G, Foster C. Monitoring exercise intensity during resistance training using the session RPE scale. *J Strength Cond Res*. 2004;18(2):353-358. doi:10.1519/R-13113.1

64. Haddad M, Stylianides G, Djaoui L, Dellal A, Chamari K. Session-RPE Method for Training Load Monitoring: Validity, Ecological Usefulness, and Influencing Factors. *Front Neurosci*. 2017;11:612. doi:10.3389/fnins.2017.00612

65. Foster C, Rodriguez-Marroyo JA, de Koning JJ. Monitoring training loads: the past, the present, and the future. *Int J Sports Physiol Perform*. 2017;12(Suppl 2):S22-S28. doi:10.1123/ijspp.2016-0388

66. Bourdon PC, Cardinale M, Murray A, et al. Monitoring athlete training loads: consensus statement. *Int J Sports Physiol Perform*. 2017;12(Suppl 2):S2161-S2170. doi:10.1123/IJSPP.2017-0208